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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,333	12/03/2001	Kathleen D. Danenberg	11220/146	5598

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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 04/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,333	DANENBERG, KATHLEEN D.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,17,20,24,25 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,17,20,24,25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on March 20, 2006 has been entered.

Priority

Applicants are advised that Applicants' claims to priority to the provisional application, 60/250,120 and 60/250,472 are **NOT GRANTED**.

The provisional application 60/250,120 (hereto referred to as the '120 application) and 60/250,472 (hereto referred to as the '472 application) do not contain proper written support under 35 U.S.C. 112, first paragraph, for the instantly claimed subject matter which pertains to the determination of metastatic cancer based on the detection of EGFR level.

The '120 application and the '472 application only contain written support for determining expression level of TS, which is thymidine synthase.

Hence the effective filing date for the instant application has been determined to be ***June 11, 2001.***

Claim Rejections - 35 USC § 112

The rejection of claims 1 and 5 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, mailed in the Office

Action mailed on February 18, 2005 is withdrawn in view of the Amendment received on March 20, 2006.

The rejection of claim 26 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, made in the Office Action mailed on February 18, 2005 is withdrawn in view of the Amendment received on March 20, 2006, canceling the claim.

Rejection, Maintained

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1, 5 , 17, 20, 24, 25, and 27 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, made in the Office Action mailed on February 18, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on March 20, 2006 have been fully considered but they are not found persuasive for the following reasons.

Applicants' arguments are addressed in the same order they were presented in the "Response to Arguments," section.

The Rejection:

Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in In Re Wands (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

Nature of the Invention & Breadth of the Claims:

The nature of the invention relates to a method for determining a chemotherapeutic regimen for treating metastatic tumor in an individual having a primary and a metastatic tumor, comprising the steps of determining the mRNA level of EGFR from a primary tumor sample and comparing this level to an mRNA level of an internal control gene; and determining a chemotherapeutic regimen for treating the metastatic tumor in the individual based on the amount of EGFR mRNA in the primary tumor sample and a predetermined threshold level for the EGFR.

Some embodiments drawn to method wherein the mRNA of EGFR extracted from fixed specimen, i.e., paraffin embedded tissue.

The breadth of the claims are drawn to a method of determining a chemotherapeutic regimen for treating metastatic tumor in an individual, by determining the mRNA level of EGFR in a primary sample and comparing this level to the mRNA of an internal control gene. The claims do not limit what is considered to be an internal control gene.

The enablement issue is as follows:

Claims are drawn to a method of determining a chemotherapeutic regimen for treating a metastatic tumor, not a primary tumor.

The enablement issue is based on whether a chemotherapeutic regimen for treating a metastatic tumor can be made based on the mRNA determination made from primary tumor sample, in the absence of any guidance in the instant specification when viewed with the guidance of the prior art.

Unpredictability & State of Prior Art:

The unpredictability in whether determining a particular chemotherapy directed toward metastatic tumor based on a primary tumor model is perhaps best expressed by Applicants' own specification:

> **To date there has been no reliable way of determining whether a particular chemotherapy directed toward the expression of a tumor gene determinant appropriate for a primary tumor is also appropriate for treating a metastsis.**

The specification sets forth the importance of determining the ***degree of variation of gene expression between primary tumors and metastases,*** wherein a significant association between levels of tumor determinant gene expression in primary tumor with expression of the same tumor determinant gene in ***matching metastases archival samples***. (page 10, lines 8-10) is purportedly reported.

The instant specification gives a working example drawn to a single tumor determinant: "significant linear correlation between TS mRNA expression in primary and secondary tumors." (page 49, lines 21-23)

This fact is also evidenced in an example wherein the specification discloses that "no significant difference between the gene expression values in the primary tumors and the metastasis," concluding that, "expression values in primary tumors accurately reflect those in metastatic tissues and thus, for patients with stage III tumors, therapy can be directed based on TS analysis in primary tumor tissue." (page 49, lines 7-12)

It should be emphasized that this working example is not drawn to what is being claimed, EGFR, but rather toward TS (thymidine synthase), wherein the primary tumor was a liver tumor.

Hence, it is plainly evident that the instant specification absolutely lacks any evidence, teaching, or guidance pertaining to whether the mRNA expression level of EGFR in primary tumor and its metastatic sample is significantly linear and that no significant difference is observed between the two. At best, the specification is prophetic in asserting that based on a single finding of a single gene expression pattern of a single tumor type, such finding can be generalized to other genes.

However, the evidence of unpredictability in whether gene expressed in a primary tumor is likely/similarly expressed without a significant difference, is replete in prior art.

Yu et al. (World Journal of Gastroenterology, 2004, vol. 10, no. 18, pages 2652-2656) evidences such unpredictability, wherein the artisans state that "[t]he differentially expressed protein of beta-globin was found in normal mucosa and hepatic metastatic tumor, but lost in primary cancer lesion." (page 2652, 1st column, Results section; and page 2655, 1st column, 2nd paragraph).

Yang et al. (Zhonghua Zhong Liu Za Zhi, 2005, vol. 27, no.1, Abstract only), evidences that while E-cadherin (E-CD) level was decreased in primary tumor samples with respect to the normal sample, the E-CD level was "significantly increased in metastatic LNs (lymphnodes)." The artisans go to express that "[t]he difference in E-CD mRNA level between metastatic LN and the primary tumor was increasing with the progression of the disease."

Finally, Scartozzi et al. (Journal of Clinical Oncology, 2004, vol. 22, no. 23, pages 4722-4778) evidences this unpredictability with respect to correlating EGFR expression in primary tumor to that of metastatic tumor:

> "[T]he detection of epidermal growth factor receptor (EFGR) expression performed in primary tumors for treatment with EGFR-targeted monoclonal antibodies could not always correlated with EGFR status in metastatic sites..." (page 4772).
> "The correlation analysis between primary cancer and corresponding metastatic sites revealed that in 19 EGFR-positive tumors (36%), the related metastatic site was EGFR-**negative** (Figure 2). On the contrary, in only seven EGFR-negative tumors (15%), cancer cells regained EGFR expression in metastasis." (page 4774, 2nd column, bottom paragraph)

The artisans even go on to state that while, "[f]ew preclinical data suggested a linear correlation between the expression of EGFR in cancer cells and response to EGFR targeted therapies...[n]evertheless, this concept **rapidly became a preconceived assumption**." (page 4775, 1st column, bottom paragraph), concluding that, "our findings showing a substantial EGFR status difference between primary tumor and related metastatic sites, suggest that the current practice of immunohistochemical analysis of any available neoplastic tissue should probably considered inadequate in non-negligible proportion of cases." (page 4777, 2nd column).

Working Examples:

The specification gives guidance so far as to guide a skilled artisan to conduct a real-time amplification of EGFR gene via use of specific primer sets (SEQ ID NO: 1 and 2) and a TaqMan™ probe of SEQ ID NO: 3 (page 37, lines 4-6) and the normalization of the EGFR expressed via use of internal control such as β-actin (page 36, lines 1-3).

The specification gives detailed information regarding the correlation between tumor gene determinant, TS (thymidylate synthase) expression in Primary and Metastases (beginning at page 48, line 20), specifically giving the mean expression values:

Source	Expression Level[1]
Primary Tumors	5.16×10^{-3}
Metastatic Tumors	4.5×10^{-3}

The specification even goes as far as giving the correlation coefficient (R^2) between TS expression values in the sets of primary and metastatic tissue, 0.95 (page 49, line 10).

The specification further states that there was a significant linear correlation between TS mRNA expression in the primary and secondary tumors (page 49, lines 17-23; Figure 1).

The specification, however, is **absolutely** silent on whether there were any correlation between the **claimed** tumor gene determinant, EGFR expression in Primary and Metastases. No expression levels whatsoever are given for EGFR for both the samples from primary and metastatic tumors. At best, the specification provides Figure 2, which illustrates how to calculate EGFR expression relative to internal control gene, which would guide a skilled artisan to calculate the expression level of EGFR in a sample. But the specification completely lacks evidence nor guidance for one skilled in the art to know that there were any correlation between primary and metastatic tumors expression EGFR.

Skill Level & Conclusion:

The skill level of the artisan in question is deemed high.

MPEP 2164.01 states that the determining enablement question is a question of law based on underlying factual findings (*In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

The fact is that the instant specification is absolutely silent in demonstrating whether the mRNA expression level found between primary tumor sample and metastatic sample is significantly the same (i.e., no significant difference).

The fact is that the art is replete with examples that show that not all genes are expressed similarly between primary and metastatic tumor samples. Particularly, Yu et al. and Yang et al. clearly demonstrate this fact.

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[1] Values from page 49, lines 6 and 7.

The fact is that the expression of EGFR between primary and metastatic tumor samples is **not** significantly the same. This fact is clearly demonstrated by Scartozzi et al., who expressly state that, "the **difference** ...[was] statistically significant." (page 4774, 2nd column, bottom paragraph to page 4775, 1st column, 1st paragraph).

Based on undisputable unpredictability coupled with the explicit teaching which evidences that the expression levels of EGFR between primary and metastatic tumors is significantly different, one of ordinary skill in the art would not be able to practice the claimed method without undue experimentation.

Response to Arguments:

Applicants' contend that the Examiner's assertion that the specification must provide a correlation between the primary and metastatic tumors of the claimed tumor gene determinant before one of skill in the art could determine the treatment of the metastatic tumor is contrary to the teachings of the specification (page 2, Response).

Applicants contend that the present invention provides a method to determine an appropriate chemotherapeutic regimen for treating metastatic tumors based upon the level of tumor gene expression from a patient derived primary tumor sample, regardless of the type of the sample (page 3, Response).

These arguments are not found persuasive because for the method to work, the expression level between the EGFR level found in primary tumor and metastatic tumor has to be substantially the same (i.e., in Applicants' words, not significantly different). As Applicants correctly state, the method determines a chemotherapeutic regimen for treating a metastatic tumor based on the level of tumor gene expression (in this case EGFR level) from a patient derived primary tumor sample.

Initially, Applicants' assumption that based on a single working example of a single gene behavior (Thymidine synthase), wherein this gene is similarly expressed between primary and metastatic tumor, is broadly applicable to other tumor genes, is fundamentally flawed.

Tumor and metastasis is driven by a complex process which involves a complex cellular response. This fact is evidenced by Yang et al. and Yu et al. who show that some of the tumor genes are not similarly expressed. Also, the fact that Scartozzi et al. explicitly demonstrate that the EGFR expression level between the primary and metastatic tumor samples factually demonstrate that therapeutic regimen based on primary tumor cannot serve as a model for its metastatic phenotype.

The arguments are not found persuasive and the rejection is maintained therefore.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent

to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Patent Examiner
Art Unit 1637
4/3/2006

YOUNG J. KIM
PATENT EXAMINER

yjk